

REMARKS

Claims 78-86 and 93-113 are pending. Claims 78, 93 and 104 have been amended to recite that the antibody or fragment “specifically binds to a B-cell,” as supported in the abstract and elsewhere. Claims 114-116 have been added based on the penultimate paragraph of the specification. Claims 78-86 and 93-116 remain in the case for further consideration.

Applicants note with appreciation that the examiner has withdrawn the rejection under the second paragraph of Section 112.

Claims 78-86, 93-108, and newly added claims 109-113 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The examiner asserts that the genus of “B-cell antibody is extremely large.” In this regard, she urges that the term “is not limited to those that bind B-cell surface proteins such as CD20; rather, B-cell antibody includes any antibody that binds proteins on surface of B-cells as well as those intracellular proteins.” Applicants have amended the main claim to recite an antibody or fragment which specifically binds to a B-cell. This limits the claim to antibodies that bind B-cell surface proteins, and more particularly to those that bind specifically, *i.e.*, that bind to one specific cell type, such as CD22. This addresses the examiner’s interpretation that the unamended claims covers an extremely large group of antibodies that includes all proteins which comprise the cell surface as well as proteins that are made intracellularly, some of which become extracellular proteins secreted by the cell. The subset of B-cell antibodies which specifically bind to a B-cell is relatively circumscribed in its scope, and fully in agreement with the teaching by applicants that antibodies that bind specifically to B cells can be used to ablate normal cells and/or treat an immune disease.

The examiner urges that “Given that there exist a large amount of B cell proteins that can be used to make B-cell antibodies, the structure of the species within the claimed genus would be expected to vary unpredictably from the structure of the single, described LL2 antibody.” However, the actual structure of the B-cell antibody is not dispositive on the issue of efficacy. What is necessary is that the B cell antibody bind specifically to the B cell. Applicant teaches that the binding of a B-cell antibody to a normal B cell will ablate that cell, thereby treating a disease associated with the B cell.

According to MPEP 2163 II.A.3a.ii., “a ‘representative number of species’ means that the species which are adequately described are representative of the entire genus.” Furthermore, “what constitutes a “representative number” is an inverse function of the skill and knowledge in the art. Satisfactory disclosure of a ‘representative number’ depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or

features of the elements possessed by the members of the genus in view of the species disclosed. For inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus.”

Here, one of skill in the art would recognize that the necessary common attribute for species within the genus is the ability to bind specifically to B cells, and also that applicant demonstrated possession of this invention. Although B cell antibodies may differ in their chemical structure, they are united in this common ability to bind specifically to B cells. The species of LL2/EPB2 that is named in the specification is representative of the genus of B cell antibodies that is claimed. The information requested by Ms. Brombeck of other antibodies that were known circa 1992 that later were shown to be effective in treating autoimmune diseases fits in with this determination of what constitutes a representative number of species with respect to the present invention, and demonstrates both the correctness and adequacy of applicant's disclosure that the genus of B cell antibodies share a commonality of function that leads to efficacy in the claimed method. It is believed that this is why Ms. Brombeck felt that such information would be highly persuasive and probative. One of skill in the art quite clearly is informed by applicant's disclosure that B cell antibodies are effective in ablating normal cells, and more particularly in treating immune diseases, and therefore possession and written description are satisfied.

Claims 93, 97-100, and newly added claim 107 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The examiner urges that the specification does not provide a written description of "a B-cell antibody or fragment thereof wherein the antibody or fragment thereof is a polyclonal, chimeric or hybrid antibody which binds multiple epitopes or antigens." However, the specification clearly describes that "Antibodies useful in the present invention may be whole immunoglobulin of any class, e.g., IgG, IgM, IgA, IgD, IgE, chimeric or hybrid antibodies with dual or multiple antigen or epitope specificities. It can be a polyclonal antibody..." In light of applicant's teaching, the skilled artisan would clearly understand that such an antibody could bind more than one epitope on a single antigen, such as CD22, or could bind to multiple B cell antigens, *e.g.*, to CD22 and CD22. Therefore, there is a written description of the subject matter recited in claims 93, 97-100 and 107.

Claims 102 and 105 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The examiner urges that these claims which use the term "B-cell immune disease" are not supported by the original disclosure or claim as filed. contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had

possession of the claimed invention for reasons of record. The specification clearly describes that the immune diseases are B-cell immune diseases. In particular, the disclosure on page 12 that LL2 targets B cells **and** is useful in treating immune disease provides a description that the immune disease is a B cell immune disease.

Claims 78-86, 93-108 and newly added and newly added claims 109-113 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement.

The examiner contends that comments were made by applicants that “only those antibodies that bind antigens well expressed on normal B cells would be effective in treating immune diseases...yet the instant claims recite any B-cell antibody or fragment thereof without considering the level of antigens that is expressed on normal B cells. Thus, one of skill in the art would not be able to make and use the claimed invention of a method of treating immune diseases using any B-cell antibodies.”¹

The comments referenced by the examiner were made by applicant with respect to Meyer. What applicant said was that “Although Meyer's results with Lym-1 and Lym-2 show some B-cell activity, these are HLA-DR antibodies. The literature clearly shows that this class of antibodies reacts with more than just B-cells, and even with some solid tumors,” and “The only species of antibodies disclosed by Meyer *et al.* are not B-cell antibodies (Meyer's characterization being inaccurate in this regard) and they are expressed only at very low levels on normal cells.” A skilled artisan does not understand the term “B-cell antibody” to include HLA-DR antibodies such as Lym-1 and Lym-2. A skilled artisan would not understand the Lym-1 or Lym-2 antibodies to be B-cell antibodies and would not select them for use in the present invention. Applicant enables the skilled artisan to use B cell antibodies which specifically bind to B-cells to ablate normal cells and treat immune disease, and was making the point that Meyer does not disclose B cell antibodies, as that term is understood by those of skill in the art.

Claims 78, 81-86, 102-105, and newly added claims 109-113 are rejected under 35 U.S.C. 102(b) as being anticipated by Meyer *et al.* (US Patent 4,861,579) for reasons of record. Claims 78,80,93,95-101, 107, and 108 are rejected under 35 U.S.C. 103(a) as being unpatentable over Meyer *et al.* (US Patent 4,861,579) in view of Sivam *et al.* (US Patent 5,116,944) for reasons of record. Claims 78 and 94 are rejected under 35 U.S.C. 103(a) as being unpatentable over Meyer *et al.* (US Patent 4,861,579) in view of Fishwild *et al.* (Nature Biotech. 1996, 14:845-851) for reasons of record.

¹ Action dated 4/23/2008, at page 15.

Meyer, cited in a rejection under Section 102 and as the primary reference in two rejections under Section 103, would not have suggested a method as presently claimed. Meyer relates to use of an anti-B cell antibody for suppressing the immune response generated upon administration of a therapeutic agent administered either as a naked or a conjugated antibody. Accordingly, there is no disclosure in Meyer that the anti-B-cell antibody is used to ablate normal cells, rather Meyer teaches how to combat the side effects arising from therapy using, for diagnostic or therapeutic purposes, an antibody (page 2, lines 38-42). The treatment modality may, according to Meyer also be used in connection with the use of therapeutic antibodies in the treatment of autoimmune diseases (page 3, lines 47-49). In other words, according to Meyer the side effects arising from the treatment of autoimmune diseases using antibodies may be treated using an antibody against the B-lymphocytes. Meyer does not teach method of ablating normal cells in a subject, comprising in which a therapeutically effective amount of a sterile injectable composition comprising a B-cell antibody or fragment thereof in a pharmaceutically acceptable injection vehicle is administered.

The examiner has responded that “in contrast to applicant's reliance on the preamble of the claims, it is noted that the claimed language or limitation does not appear to result in a manipulative difference in the method steps when compared to the prior art disclosure.” Applicant has amended claim 78 to recite *in the body of the claim* “thereby to ablate the normal cells” and has amended claim 104 to recite “thereby to treat the immune disease.” This addresses the statement that applicant is relying on the preamble. Furthermore, the Lym-1 and Lym-2 antibodies of Meyer do not *specifically bind to B-cells*, thereby to ablate normal cells or treat an immune disease, as in the amended claims.. They are administered to alleviate the side effects of using a therapeutic antibody to treat a disease, and not to ablate cells or treat an immune disease.

Claims 78, 79, 81, 93, 102-107, and newly added claims 109-113 are rejected under 35 U.S.C. 102(b) as being anticipated by Bussel et al. (Blood 1988 72;1: 121-127) as evidenced by de Grandmont et al. (Blood 2003 101;8:3065-3073) for reasons of record. As noted previously, de Grandmont *et al.* discusses the role of the Fc region of IVIG in treatment, as mentioned on page 3065 of that document, and fails to teach that IVIG includes B cell antibodies, let alone teaching or suggesting the use of B-cell antibodies in ablating normal cells in a subject. The primary mechanism of IVIG has been proposed to be the blockade of Fc-receptors, as reported in Teeling *et al.*, “Therapeutic efficacy of intravenous immunoglobulin preparations depends on the immunoglobulin G dimers: studies in experimental immune thrombocytopenia,” *Blood*, 2001, Aug 15;98(4):1095-9, and applicant's previous comments are incorporated here by reference. Certainly

the fact that Fc-fragments have the same activity in patients as IVIG goes against an assertion of any possible antibody effect of the preparation.

Even assuming, *arguendo*, that IVIG does include B-cell antibodies, it is clear that the amount is not sufficient to anticipate a claim which recites "a therapeutically effective amount" of B-cell antibody. The art clearly shows that the therapeutically active ingredient in IVIG is dimers interacting with Fcγ receptors, not B-cell antibodies. Accordingly, the rejection under Section 102(b) based on Bussel *et al.* as evidenced by de Grandmont *et al.* is *prima facie* defective and reconsideration and withdrawal is respectfully requested.

In response to the examiner's comments, the claims have been amended to recite a B-cell antibody which specifically binds to a B-cell, and claims also have been added which recite that the antibody is specific to a marker associated with a B cell. De Grandmont does not teach a B-cell antibody which specifically binds to a B-cell.

Reconsideration and withdrawal of all art-based rejections is therefore respectfully requested.

In view of the foregoing, it is believed none of the references, taken singly or in combination, discloses the claimed invention, and therefore a notice of allowance is respectfully requested. If there are any problems with this response, applicant requests a further interview with the examiner, her supervisor and Ms. Brumbeck.

Respectfully submitted,

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